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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,377	07/10/2001	Keith D. Allen	R-365	8328
26619	7590	02/07/2005	EXAMINER	
DELTAGEN, INC. 1031 Bing Street San Carlos, CA 94070			TON, THAIAN N	
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			1632	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/903,377	<b>Applicant(s)</b> ALLEN, KEITH D.	
	<b>Examiner</b> Thaian N. Ton	<b>Art Unit</b> 1632	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 1/14/05.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 31-34,38 and 40-43 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 31-34,38 and 40-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/05, has been entered.

Applicants' Amendment, filed 1/14/05, has been entered. Claims 1-30, 35-37 and 39 are cancelled. Claims 31, 32, 34 and 38 have been amended. Claims 40-43 have been added. Claims 31-34, 38, 40-43 are pending and under current examination.

### *Claim Rejections – 35 USC §101 & 112*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Definitions:

[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from <http://www.uspto.gov/web/menu/utility.pdf> ]

Art Unit: 1632

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 31-34, 38, 40-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for reasons of record advanced in the prior Office actions.

The claims, as instantly amended, are directed to a transgenic mouse whose genome comprises a null chemokine receptor 9A allele, wherein said null allele comprises exogenous DNA. In further embodiments, the transgenic mouse exhibits decreased performance on an accelerating rotarod relative to a wild-type mouse, cells obtained from said mouse, methods of producing said mouse.

Applicants traverse the prior rejection, point to the MPEP to support that the Office should presume a statement of utility made by application is true, point that rejections under 35 U.S.C. 101 have been rarely sustained by federal courts, and that the burden is on the Examiner to show that one of ordinary skill in the art would find the asserted utility to be false. See pp. 4-6 of the Response. Applicants argue that the present invention has a well-established utility because one of ordinary skill in the art would "immediately appreciate why" knockout mice are useful, namely, because the mice have an inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the claimed knockout mice. Applicants point to the NIH to support that knockout mice represent a critical tool in studying gene function. See pp. 6-7 of the Response. Finally, Applicants argue that knockout mice are so well-accepted as tools for

determining gene function, that various individuals have proposed creating knockout mice for all genes. See p. 7 of the Response. Applicants argue that which respect to the claims drawn to transgenic mice having a null allele, Applicants provide Austin *et al.*, who state that null-reporter alleles should be created, that they are an, "indispensable starting point for studying the function of every gene." Further, Applicants argue that research tools, such as the instantly claimed knockout mice, are patentable because they have a clear, specific and unquestionable utility, which is to analyze gene function. Applicants further argue that various authors provide support for the asserted utility of the claimed mice, for example, Alberts *et al.* provide teachings to show that knockout mice are "invaluable tools for investigating gene function," Genes VII states that knocking out of a gene is, "[A] powerful method to investigate directly the importance and function of the gene." See pp. 8-9 of the Response. Applicants further argue that the commercial use of the knockout mice has been clearly established because a large pharmaceutical company has ordered the claimed transgenic mice, and that it cannot be reasonably argued that the claimed invention has no "real world use". Applicants submit that one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, and that this utility is found to be specific, substantial, and credible. See p. 10 of the Response. This is not persuasive. In the instant case, the claimed knockout mice lack utility for the reasons set forth in the previous Office actions. For example, knockout mice may

not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. However, the contemplated utilities of using the instant mice to obtain a clue to a pathway is not a considered "substantial utility." Note that it was scientifically well-known to knock out a gene to determine its function or what will happen when the gene is not expressed. This is supported further by Applicants' response. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility. The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial, specific or credible. With respect to MPEP §2107.01, I (see p. 6 of Applicants' Response), a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

The utility guidelines specifically state that further research is not a "substantial utility":

[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of Applicants' invention as a model of disease, particularly, because the instant specification fails to disclose any specific disease or condition that is associated with the disruption of a chemokine receptor 9A allele. Further, note that it is clear from all of the art provided by Applicants that knockout mice are used to elucidate gene function, which is not considered a substantial utility.

The asserted utility is not considered to be specific and substantial because the evidence of record has not provided a correlation between a disruption of a chemokine receptor 9A allele and the claimed phenotype of decreased performance on an accelerating rotarod, characterized by falling from an accelerating rotarod at lower speeds relative to a wild-type mouse; thus, the asserted utilities of the mice is not apparent. As stated previously, the instant specification fails to adequately demonstrate or teach that the response of the claimed transgenic mouse is due to decreased agility, coordination, or balance. See p. 3 of the prior Office action. The

evidence and teachings of record fail to provide a nexus between a chemokine receptor 9A allele and any particular disease or disorder associated with it. Furthermore, neither the specification nor any evidence or teachings of record have provided any other utilities for the claimed transgenic mice that are specific and substantial. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claims. Thus, using the mice claimed for further research is not a "substantial utility".

Applicants argue that in the prior Office action, the Examiner argues that the claimed phenotypes do not correlate with a specific disease, and further, that the Examiner supports this conclusion by noting that the ranges in Table 1 overlap and that the difference between the wild-type and knockout mouse is not significant, that the Examiner suggests that the phenotype was not caused by the disruption of a chemokine receptor 9A allele. Applicants assert that the instant case is similar to arguments made in *In re Brana*. Applicants argue that the claimed invention is useful for a practical purpose (to determine the function of the chemokine 9A receptor gene), and that this assertion would be considered credible by a person of ordinary skill in the art; because the claimed mice have demonstrated specific phenotypes (decreased performance on an accelerating rotarod, characterized by falling from an accelerating rotarod at lower speeds relative to a wild-type mouse) and the use of these mice would be considered to be

for determining how the chemokine 9A receptor affects rotarod performance. Applicants cite art to show that knockout phenotypes provide accurate information concerning gene function (Doetschman). See pp. 11-13 of the Response.

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention. Furthermore, it is reiterated that the instant invention does not have utility because the mice exhibit a phenotype that fails to be correlated to the function of the chemokine 9A receptor. There is no correlation between the observed phenotypes and the knockout of the chemokine 9A receptor gene; thus the utility of these mice are not readily apparent.

Applicants argue that the cited art of record, Crabbe and Rustay were improperly applied. Firstly, that Crabbe do not specifically teach inconsistency for

the rotarod test. This argument was addressed in the prior Office action that Crabbe was used to support that the behavioral phenotype of a knockout mouse is dependent upon the laboratory environment, as well as the genetic background of the mice. Applicants argue that Rustay conclude that, "Strain performances were highly consistent both between and within laboratories." Further, Applicants argue that Rustay encourages the use of the rotarod in evaluating motor coordination in mice, and that the data disclosed by Rustay do not demonstrate a difference in rotarod performance among strains, that the conclusions drawn by Rustay relate to testing the effect of ethanol on rotarod performance, and finally, that Rustay does not demonstrate that one of skill in the art would doubt Applicants' phenotypic conclusions. See pp. 14-15 of the Response.

This is not found to be persuasive. Applicants point to a particular section of Rustay to support that there are no strain differences between inbred mice. What Rustay states, cited from the entire paragraph is that, "... 21 strains of mice were tested in two separate laboratories to assess inter- and intralaboratory genetic reliability of the ARR data. Strain performances were highly consistent both between and within laboratories (Fig. 2, Table 3)." (See p. 2920, 2<sup>nd</sup> column, 1<sup>st</sup> ¶, emphasis added). Thus, when Rustay states that strain performances on the ARR were consistent, they are referring to the fact that among the 21 strains of mice tested, the 21 strains showed consistent performance when comparing each strain to itself, not to other strains. This is further stressed when they note that a few

strains showed different acquisition of the rotarod performance in Portland and Edmonton. Furthermore, it is evidenced in Figure 2 and Table 3 that there is an extreme amount of variability between different strains. With regard to Applicants' pointing to Table 1, Figure 1 and Figure 2, as support to show that only one strain exhibited a significant difference, this is not persuasive. Rustay states, with regard to Figure 1 that, "There was a wide range of performance among strains when tested at 20 rpm/min; however, at 60 rpm /min, there was less variation among strain." See p. 2919, 2<sup>nd</sup> column, 1<sup>st</sup> ¶. It is clear that Rustay teaches that strain differences affect rotarod performance, because they state that inbred mice have differences in acquisition, retention, and peak rotarod performance, which they suggest are likely to reflect differences in structure and/or function of essential brain regions. See p. 2921, 2<sup>nd</sup> column, Discussion, 3<sup>rd</sup> ¶. Although Applicants argue that the claimed phenotypes are specific to the claimed mouse, it is reiterated that a phenotype specific to a mouse does not render the utility of the mouse specific. The claimed phenotype is not specific to any disease or disorder such that there would be a specific use for the mouse.

Applicants argue that in addition for studying gene function, the claimed transgenic mice are useful for studying gene expression. The claims as amended now recite that the transgenic mice contain a visible marker, such as lacZ. Applicants cite Austin *et al.* to support that studying gene expression using a reporter gene is clearly recognized by those skilled in the art. Further, Applicants

remind the Examiner that the claimed invention need only satisfy one of its stated objectives to satisfy the utility and enablement requirements. See pp. 12-13 the Response.

This is not persuasive. In particular, utilizing a visible marker, such as lacZ is a general utility that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter gene into an endogenous gene. Just as any gene can be cloned to study gene expression, any gene can be knocked out using a lacZ construct to study function and/or expression.

Thus, it is maintained that neither specification, nor the art of record provides evidence of the existence of a correlation between decreased agility, coordination or balance and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse encompassed by the claims. The specification essentially provides an invitation to experiment, wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claim. Thus, the skilled artisan would not find the asserted utility of the claimed transgenic mice to be specific and substantial.

Claims 31-34, 38, 40-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons

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set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was

made, it would have required undue experimentation to make and/or use the invention as claimed.

The claims are directed to transgenic mice whose genome comprises a null chemokine receptor 9A allele, wherein the null allele comprises exogenous DNA, and the mouse exhibits the phenotype of decreased performance on an accelerating rotarod, characterized by falling from an accelerating rotarod at lower speeds relative to a wild-type mouse; cells, and methods of producing said mice.

The specification states that the targeting construct was introduced into 129/SvEv mouse substrain embryonic stem cells to produce chimeric mice. The specification continues to states that F1 mice were generated by breeding with C57BL/6 females, and F2 homozygous mice were produced by intercrossing F1 heterozygous males and females. Specification, page 55. It was found that the these mice, when compared to age and gender-matched wild-type control mice, homozygous mutant mice exhibited decreased agility, coordination, or balance, as characterized by decreased performance on an accelerating rotarod.

In attempting to determine gene function through an analysis of behavioral or physiological testing of mice comprising a disruption of a gene, in this case a gene encoding chemokine receptor 9A, distinguishing between a phenotype that is a result of gene loss and genes of the parental strains becomes problematic. In the production of the presently claimed mice, the specification, as outlined above states that the recombination construct is injected into a 129/SvEv ES cell, which is in

turn injected into a C57BL/6 blastocyst. The chimeric blastocysts are then transferred to a C57BL/6 female for gestation. Chimeric mice are mated to produce F1 heterozygous mice and F1 heterozygous mice are mated to produce F2 homozygous mice. However, as it is well established in the art, the homozygous mice claimed will have some 129/SvEv genes, regardless of the outward appearance of the mice due to the 129 knockout construct. F2 mice homozygous for the disrupted chemokine receptor 9A gene have genotypes from two parents, 129/SvEv and C57BL/6, due to recombination events during gametogenesis (Gerlai, **Trends in Neuroscience**. 19:177-181 (1996); see page 178, lines 1-5). These mice are genotypically different from wild-type littermates, and thus wild-type littermates are not good controls for the null mice (Gerlai, page 178, col. 1, lines 6-18). This effect causes "linkage disequilibrium between the transgene and surrounding genes, producing a "hitchhiking donor gene confound" (Lariviere, **J. Pharmacology Experiment. Therapeut.**, 297: 467-473 (2001); see page 468, col. 1, parag. 2, lines 1-4). To overcome the "hitchhiking effect, two remedies are suggested: testing a large number of mice (Gerlai, page 178, col. 2, lines 1-5) and many backcrosses (Lariviere, page 468, col. 1, parag. 2, line 18-21). However, even with a large testing population and multiple backcrossings, some of the 129/SvEv genome will remain. Thus, the behavioral and physiological effects observed in the presently claimed Chemokine receptor 9A null mice could be due to 129/ SvEv genes (Gerlai, page 179, col. 1, lines 9-14). There is no way to tell given the tests in the disclosure. Thus, determining

whether or not the phenotype of the mice seen is due to disrupted gene, the 129 “hitchhiking” alleles or compensation by other C57Bl genes cannot be determined from applicant’s data.

Therefore, there is no enabled use for the claimed mice as the phenotypes disclosed and claimed for the mice are not predictably correlated to the function of the chemokine receptor 9A gene, as taught by the art, and mice are not taught to have a phenotype that correlates to any disease or condition. No other uses of the mice are disclosed. Finally, as amended, certain of the claims fail to provide an appropriate phenotype for the claimed mice. See, for example, claim 31. Thus, without an appropriate phenotype, one of skill in the art would not know how to use these claimed mice. Note that enablement requires both how to make and how to use the claimed invention.

Claim 34 is to a cell from a mouse comprising a disruption of the chemokine receptor 9A gene. This cell will not have any of the phenotypes of the mice from which the cells were isolated, and thus it is not clear the phenotype of cells. Therefore, the use of the cells in a drug-screening assay to identify agents that affect chemokine receptor 9A gene expression or function or affects any of the particular disclosed phenotypes is not enabled.

Claim 38 is further not enabled because it recites that a mouse embryonic stem cell is introduced into a pseudopregnant mouse. This reads on direct implantation of any type of mouse ES cell anywhere in a pseudopregnant mouse. It

is well known in the art that a transgenic mouse is made by introducing a mouse ES cell into a mouse blastocyst and implanting the blastocyst into the uterus of a pseudopregnant female mouse.

The specification fails to enable disrupting any chemokine receptor 9A gene in a mouse. The breadth of the claims encompasses chemokine receptor 9A genes other than that described and set forth by SEQ ID NO:1. The evidence of record teaches only one chemokine receptor 9A sequence (SEQ ID NO:1). The specification does not provide adequate guidance for determining any other chemokine receptor 9A genes since there is no assay for activity of the gene or the encoded protein. Therefore, the specification only enables making a transgenic mouse whose genome comprises a disruption the chemokine receptor 9A gene set forth by SEQ ID NO:1.

Therefore, the skilled artisan would have been required to engage in an undue amount of experimentation at the time of filing to implement the invention as claimed.

Claims 1 and 93-158 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

The specification has described the nucleotide sequence encoding a chemokine receptor 9A gene as set forth by SEQ ID NO: 1. In the instant case the genus of chemokine receptor 9A genes encompassed by the claims lack a written description. The specification fails to describe what DNA molecules other than the nucleotide sequence set forth in SEQ ID NO: 1 fall into this genus. There is no description providing evidence of possession at the time of filing for homology to chemokine receptor 9A. Therefore, description of SEQ ID NO: 1 fails to fulfill the written description requirement for the claimed genus because one could not have envisioned the primary structure of other nucleotides encoding the gene. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of chemokine receptor 9Agene other than that set forth by SEQ ID NO:1. Therefore, only the chemokine receptor 9Agene encompassed by SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention

and do so in sufficient detail that one skilled in the art can clearly conclude that “the inventor invented the claimed invention”.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 is are vague as to the metes and bounds of the claims. The claim states “a cell”, which encompasses a cell in the mouse. This embodiment is not contemplated by the specification. From a reading of the specification, the cells are meant to be “isolated.” The claims should be amended to state “an isolated cell.”

Claim 38 is unclear. Claim 38 states that a pseudopregnant mouse gives birth (see step (c)). A pseudopregnant mouse is not pregnant; she only appears pregnant. Appropriate correction is required.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31, 34, 38, 40, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi *et al.* [Scientific American, 1994, 270:34-41] when taken with Zaballos *et al.* [The Journal of Immunology, 162:5671-5675 (1999), cited on Applicants' IDS filed 5/7/03] as evidenced by Genbank Accession Number: NM\_009913.

Note that absent any phenotypic requirements of the claimed transgenic mice, the combination of the cited prior art is sufficient to make obvious the invention, further note that it would be well-known in the art that the disruption of any gene of interest, at any particular exon would have a reasonable expectation of decreased expression of that particular gene.

Capecchi teaches knockout technology applied to mice, specifically with respect to the disruption of the *HoxA-3* gene and as a method of producing the same, applies to determining the *in vivo* biological function of any known gene of interest. For example, Capecchi discloses the applicability of gene targeting to many other genes, so that a correlation can be drawn between the malfunctioning

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gene to the manifestation of disease [see p. 41, col. 2, 2<sup>nd</sup> full paragraph]. Capecchi further discloses the essential components of a targeting vector [p. 38, col. 3, and p. 39, col. 1-2], and the steps involved for targeted gene replacement in ES cells as well as in mice [see p. 36-39 and diagrams]. Capecchi differs from the claimed invention in that the targeting construct does not contain flanking nucleotide sequences which homologous recombine with the chemokine receptor 9A gene. However, prior to the time of the claimed invention, Zaballos teach the sequence of the mouse CCR9 gene. This is evidenced by the Genbank Accession Number NM\_009913 (which cites Zaballos) and provides the sequence of the CCR9 gene.

Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Capecchi by use of a targeting vector for the disruption of the known chemokine receptor 9A, gene in a mouse with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to make such a modification, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse, as supported by Capecchi who teach that the generation of mouse models will allow for the observation of effect of a knocking out a particular gene on disease phenotypes. See p. 41, 2<sup>nd</sup> column, 2<sup>nd</sup> ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.


*Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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